

The Liability Threshold Model for Censored Twin Data

Klaus K. Holst^{a,*}, Thomas H. Scheike^a, Jacob B. Hjelmborg^b

^a*Dept. of Biostatistics, University of Copenhagen, Denmark*

^b*Dept. of Epidemiology, Biostatistics and Biodemography, University of Southern Denmark, Denmark*

Abstract

Family studies provide an important tool for understanding etiology of diseases, with the key aim of discovering evidence of family aggregation and to determine if such aggregation can be attributed to genetic components. Heritability and concordance estimates are routinely calculated in twin studies of diseases, as a way of quantifying such genetic contribution. The endpoint in these studies are typically defined as occurrence of a disease versus death without the disease. However, a large fraction of the subjects may still be alive at the time of follow-up without having experienced the disease thus still being at risk. Ignoring this right-censoring can lead to severely biased estimates. The classical liability threshold model can be extended with inverse probability of censoring weighting of complete observations. This leads to a flexible way of modelling twin concordance and obtaining consistent estimates of heritability. The method is demonstrated in simulations and applied to data from the population based Danish twin cohort to describe the dependence in prostate cancer occurrence in twins.

Keywords: Liability-threshold; Random effects; Probit model; Cumulative Incidence; Right censoring; Competing risks; Polygenic model; Twins; Heritability

1. Introduction

Family studies provide an important tool for understanding etiology of diseases, with the key aim of discovering evidence of family aggregation and to determine if such aggregation can be attributed to genetic components. Heritability and concordance estimates are routinely calculated in twin studies of diseases, as a way of quantifying such genetic contribution. As a key paper for studying heritability of cancer, Lichtenstein et al. (2000) reported heritability estimates for prostate cancer of 0.42 (95% confidence limits 0.29–0.50) and casewise concordance of 0.21 in monozygotic (MZ) twins and 0.06 in dizygotic (DZ) twins based on combined cohorts of 44,788 twin pairs from the Nordic twin registries. This suggests a considerable genetic contribution to the development of prostate cancer. A polygenic liability threshold model, i.e., a Probit variance component model, was used to

*Corresponding author. Tel.: +45 35327901

Email address: k.k.holst@biostat.ku.dk (Klaus K. Holst)

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quantify the heritability on the liability scale from the classification of subjects as cancer cases or non-cancer cases (died without cancer). However, a large fraction of the twin-pairs were still alive at the end of follow-up but treated as non-cancer case. This corresponds to treating this part of the population as immune to cancer, suggesting that the estimates of the targeted population parameters in this study could be severely biased. The censoring mechanism has largely been ignored in the epidemiological literature of family studies, which unfortunately makes reported estimates of both heritability, and other population parameters of interest such as concordance probabilities, very difficult to interpret.

The key to solving this problem is to consider the event times in the analysis. Standard techniques for correlated survival data are not appropriate here, due to the competing risk of death. Dependence on the hazard scale while taking possible dependence between causes into account has been considered by Ripatti et al. (2003) and Gorfine and Hsu (2011). Scheike et al. (2014a) considered dependence on the probability scale via random effects models and Scheike et al. (2014b) examined non-parametric estimates of the concordance function, i.e., the probability of both twins experiencing cancer before a given time point. These methods yield constructive ways of analysing twin data of disease status, however, care in correctly specifying the dependence structure over time via the random effects structure has to be taken. Furthermore, none of the approaches provide heritability estimates that are comparable with the classical definition of heritability on the liability scale given by Falconer (1967). In the following we will define a simple estimator which gives consistent concordance estimates and estimates of heritability on the liability scale under independent right-censoring.

The paper is structured as follows. In Section 2 we review basic concepts in quantitative genetics and define heritability with the aim of estimating the degree of association due to genes and environmental factors through random effects modelling. In particular, we note that dependence on the probability scale is something quite different from dependence on the normal scale. We introduce the competing risks framework and present the inverse probability of censoring weighted estimating equations in Section 3. The method is demonstrated in simulations in Section 4. A worked example based on the Danish twin registry is presented in Section 5 followed by a general discussion.

2. Polygenic models

The basic idea of family-studies of a quantitative trait is to exploit that stronger phenotypic resemblance will be seen between closely related family members when the trait is genetically determined. In particular, for twin studies we may exploit that monozygotic (MZ) twins in principle are genetic copies whereas dizygotic (DZ) twins genetically on average resembles ordinary siblings. This allows us under appropriate genetic assumptions to decompose the trait into genetic and environmental components, $Y = Y_{\text{gene}} + Y_{\text{envir}}$, which may be modelled using random effects. Assuming independence between genetic and environmental effects the *broad-sense heritability* may then be quantified as the fraction of the total variance due to genetic factors.

The theoretic foundation in modern quantitative genetics was laid out in the pioneering work of Fisher (1918) who formally described the above genetic decomposition in terms of additive and dominant genetic effects. Familial resemblance may be defined from the *kinship-coefficient* Φ_{jk} which is the probability that two randomly selected alleles from the same locus of relatives k and j are *identical by descent*, i.e., the alleles are physical copies of the same gene carried by a common ancestor. Under assumptions of random mating (no inbreeding), linkage equilibrium, no gene-environment interaction and epistasis, and parents do not transmit their environmental effects to their children, this leads to a covariance between the observed phenotypes Y_k and Y_j for the relatives given by

$$\text{Cov}(Y_k, Y_j) = 2\Phi_{kj}\sigma_A^2 + \Delta_{7kj}\sigma_D^2 + \sigma_C^2,$$

where the identity coefficient Δ_{7kj} describes the probability that at a given loci both alleles for the two relatives are identical by descent (Lange, 2002). The variance components σ_A^2 describes the additive genetic effects, σ_D^2 the dominant genetic effects and σ_C^2 describes variance of shared environmental effects for the two relatives.

This can be captured in a random effects model where the polygenic phenotype Y_{ij} may be modelled as

$$Y_{ij} = \beta^T X_{ij} + \eta_{ij}^A + \eta_i^C + \eta_{ij}^D + \varepsilon_{ij}, \quad (1)$$

for family $i = 1, \dots, n$ and family member $j = 1, \dots, K$ with covariates X_{ij} . Here we assume that there is the same shared environmental effect for all family members. All the random effects are assumed to be independent and normally distributed which in general may be reasonable for polygenic traits (Lange, 1997)

$$(\eta_{ij}^A, \eta_i^C, \eta_{ij}^D, \varepsilon_{ij})^T \sim \mathcal{N}(0, \text{diag}(\sigma_A^2, \sigma_C^2, \sigma_D^2, \sigma_E^2)).$$

The residual terms ε_{ij} are assumed to be iid normal and the variance component σ_E^2 may be interpreted as the variance of the unique environmental effects. The (broad-sense) heritability may then be defined as

$$H^2 = \frac{\sigma_A^2 + \sigma_D^2}{\sigma_A^2 + \sigma_C^2 + \sigma_D^2 + \sigma_E^2}.$$

For MZ twins we have $\Phi_{kj}^{\text{MZ}} = \frac{1}{2}$ and $\Delta_{7kj}^{\text{MZ}} = 1$ and for DZ twins $\Phi_{kj}^{\text{DZ}} = \Delta_{7kj}^{\text{DZ}} = \frac{1}{4}$, hence

$$\begin{aligned} \text{Cov}(Y_{i1}^{\text{MZ}}, Y_{i2}^{\text{MZ}}) &= \begin{pmatrix} \sigma_A^2 + \sigma_C^2 + \sigma_D^2 + \sigma_E^2 & \sigma_A^2 + \sigma_C^2 + \sigma_D^2 \\ \sigma_A^2 + \sigma_C^2 + \sigma_D^2 & \sigma_A^2 + \sigma_C^2 + \sigma_D^2 + \sigma_E^2 \end{pmatrix}, \\ \text{Cov}(Y_{i1}^{\text{DZ}}, Y_{i2}^{\text{DZ}}) &= \begin{pmatrix} \sigma_A^2 + \sigma_C^2 + \sigma_D^2 + \sigma_E^2 & \frac{1}{2}\sigma_A^2 + \sigma_C^2 + \frac{1}{4}\sigma_D^2 \\ \frac{1}{2}\sigma_A^2 + \sigma_C^2 + \frac{1}{4}\sigma_D^2 & \sigma_A^2 + \sigma_C^2 + \sigma_D^2 + \sigma_E^2 \end{pmatrix}. \end{aligned}$$

Note that one consequence of the model is that MZ and DZ twins follow the same marginal distribution. Unfortunately, the classic twin design does not allow identification of all variance components. Further inclusion of other family members or twin-adoptives can remedy

this problem, but may further complicate assumptions regarding shared/non-shared environmental effects across different family members. The pragmatic solution is typically to report results from the most biologically relevant model, i.e., for certain traits the shared environmental effect may be known to be negligible, or to choose a sub-model based on some model selection criterion (Akaike, 1973). For the classical twin design omitting one variance component in the above formulation (typically the dominant genetic component, leading to the so-called ACE-model), the Maximum Likelihood Estimates can be obtained using specialised software for family studies (Holst and Scheike, 2014) or any general Structural Equation Model implementation.

2.1. Liability threshold model

For binary traits the classical polygenic model (1) may be extended by a model of the form

$$g(\mathbb{P}(Y_{ij} = 1 \mid X_{ij}, \eta_{ij}^A, \eta_i^C, \eta_{ij}^D)) = \beta^T X_{ij} + \eta_{ij}^A + \eta_i^C + \eta_{ij}^D, \quad j = 1, 2, \quad (2)$$

where g is some link-function, X_{ij} are possible covariates that we wish to adjust for, and $\eta_{ij}^A, \eta_{ij}^C, \eta_{ij}^D$ are random effects. Using the Probit link (Falconer, 1967; Falconer and Mackay,

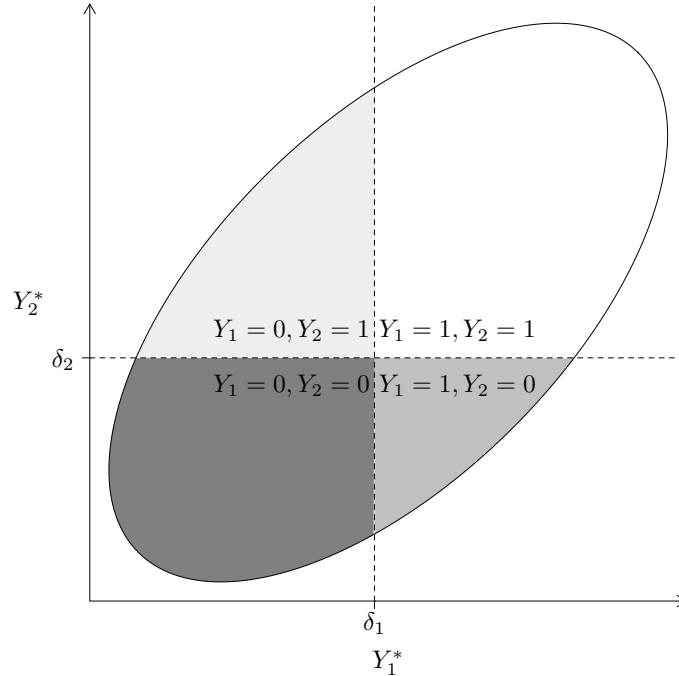


Figure 1: Liability threshold model where the observed binary pair (Y_1, Y_2) is a realization defined from underlying unobserved continuous variables (Y_1^*, Y_2^*) such that $Y_k = 1$ exactly when the *liability* Y_k^* exceeds some threshold δ_k .

1996; Neale and Cardon, 1992; Sham, 1998) Equation (2) gives the *Liability Threshold*

Model and has been widely adopted, since this leads to a model equivalent to (1) for a latent Gaussian variable (see Figure 1)

$$Y_{ij}^* = \beta^T X_{ij} + \eta_{ij}^A + \eta_i^C + \eta_{ij}^D + \varepsilon_{ij}, \quad j = 1, 2,$$

where we only observe the thresholded version

$$Y_{ij} = \begin{cases} 1, & Y_{ij}^* \geq \delta_j \\ 0, & Y_{ij}^* < \delta_j. \end{cases}$$

For identification, the threshold is fixed at $\delta_j = 0$ and the variance of the residual term ε_{ij} set to one. On the Probit-scale this corresponds to

$$\mathbb{P}(Y_{ij} = 1 \mid X_{ij}, \eta_{ij}^A, \eta_i^C, \eta_{ij}^D) = \Phi(\beta^T X_{ij} + \eta_{ij}^A + \eta_i^C + \eta_{ij}^D), \quad (3)$$

noting that the E component is modelled indirectly through the inverse link-function Φ which is the standard normal CDF, i.e., $\sigma_E^2 = 1$. In the following we will simplify notation and use η_{ij} to denote the total random effect for the j th twin in the i th twin-pair.

Note that the corresponding heritability in this model

$$H^2 = \frac{\sigma_A^2 + \sigma_D^2}{\sigma_A^2 + \sigma_C^2 + \sigma_D^2 + 1},$$

relates to the underlying liability scale, and that there are additional variation present in the data on the risk scale. Using only the random effects to define a heritability estimate is thus not comparable to the one from the standard normal model, where all the variation is included in the heritability estimate.

The Probit random effects analyses have been criticized for completely ignoring the time-aspect and the fact that the analyses did not take censoring into account (Duncan, 2004). In Lichtenstein et al. (2000) the analysis was based on the assumption that the probability of occurrence of cancer for twin j in twin pair i was on the same form as (2) with

$$\mathbb{P}(\text{twin } j \text{ gets cancer} \mid \eta_{ij}) = \Phi(\eta_{ij}), \quad j = 1, 2, \quad (4)$$

and with the complementary outcome being that the twin died without getting cancer or still was alive and without cancer at the time of follow-up. The latter group are thus treated as immune to cancer after they leave the study, which in general makes the results of the analysis impossible to interpret. The right-censoring mechanism therefore has to be taken into account, but additional information on the timing of the events are needed. In practice, these event times are typically readily available in family studies of disease.

3. Inverse Probability of Censoring Weighted Estimating Equation

The definition of the liability threshold model perceives the states “prostate cancer” and “death” as static endpoints. Our aim of adjusting the estimating procedure for the

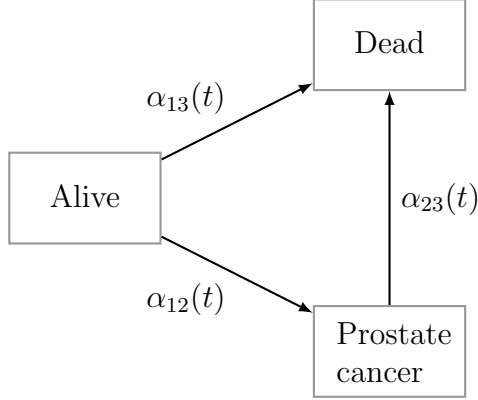


Figure 2: Competing risks model for the two competing risks of death and prostate cancer with the transition probabilities being described by the cause-specific hazards $\alpha_{kl}(t)$.

right-censoring, however, requires us to consider the data in a dynamic framework. A more natural setting for the data generating mechanism is to consider the problem in the competing risk setting. In the following let $(T_{ik}, C_{ik}, \epsilon_{ik}, X_{ik})$ denote the event time, right censoring time, the cause of failure $\epsilon_{ik} \in \{1, \dots, J\}$ (e.g., cancer or death without cancer), and p -dimensional covariate vector X_{ik} for twin pair $i = 1, \dots, n$ and individual $k = 1, 2$. We will assume that the n pairs $\{T_i, C_i, \epsilon_i, X_i\} = \{\{T_{i1}, T_{i2}\}, \{C_{i1}, C_{i2}\}, \{\epsilon_{i1}, \epsilon_{i2}\}, \{X_{i1}, X_{i2}\}\}$ are iid. Due to the right-censoring, we only observe $\tilde{T}_{ik} = T_{ik} \wedge C_{ik}$ and $\tilde{\epsilon}_{ik} = \epsilon_{ik} \Delta_{ik}$, with the indicator for T_{ik} denoting an actual event time $\Delta_{ik} = I(T_{ik} \leq C_{ik})$. We will perceive the data as generated by the model described by the diagram in Figure 2, where every subject starts in the alive state, and then moves to either of the two states prostate cancer or death with certain intensities evolving over time. Note that in our application, we are not aiming to make inference on the transition from prostate cancer to death.

In the univariate setting, the transition may be characterized by the cumulative incidence functions

$$F_1(t) = \mathbb{P}(T \leq t, \epsilon = 1),$$

which may be estimated by the Aalen-Johansen estimator (Aalen and Johansen, 1978; Andersen et al., 1993) and also generalized to the regression setting as in Scheike et al. (2008). The bivariate case is more complex but the concordance function

$$\mathcal{C}(t) = \mathbb{P}(T_1 \leq t, T_2 \leq t, \epsilon_1 = 1, \epsilon_2 = 1),$$

may be estimated as described in Scheike et al. (2014b). Here we will only consider a fixed time τ and characterize the joint probability

$$\mathbb{P}(T_1 \leq \tau, T_2 \leq \tau, \epsilon_1 = 1, \epsilon_2 = 1), \quad (5)$$

which we will assume can be modelled by a random effect structure as in (3)

$$\mathbb{P}(T_{ij} \leq \tau, \epsilon_{ij} = 1 | \eta_{ij}, X_{ij}) = \Phi(\beta^T X_{ij} + \eta_{ij}). \quad (6)$$

We will use age as our time-scale, and assuming that everyone were followed until time τ this simply corresponds to a standard liability model where twins are classified as having cancer or not before time τ , in which case the standard MLE approach of (3) would be consistent. In practice, a large fraction of the twins may not have reached the age τ at the end of follow-up, and other techniques must be applied.

3.1. Consistent Estimating Equations

In this section we will introduce inverse probability weighting to correct for the right censoring. The intuition for this procedure is that the observations that have a higher probability of being censored are under-represented and should therefore count more in the analysis. These techniques can be traced back to the Horvitz-Thompson estimator applied in the survey-statistics field (Horvitz and Thompson, 1952) and later with many applications in other fields of statistics for dealing with coarsened data including survival analysis (Rotnitzky and Robins, 1995; Robins and Rotnitzky, 1992) and competing risks (Fine and Gray, 1999). We refer to Tsiatis (2006) for a modern and accessible treatment of the subject in both the parametric and semi-parametric setting. Here we are interested in estimating dependence between paired observations which in general complicates the analysis, due to the need of consistent estimates of the bivariate censoring probabilities. We will show how the complexity may be reduced dramatically by exploiting how data is collected in registry studies.

The full-data score equation we obtain from the model (6) parametrised by θ (including both β and the parameters of the random effects), when all subjects are followed until time τ , will be denoted

$$\mathcal{U}_0(\theta; X, \tilde{T}, \tilde{\epsilon}) = \sum_{i=1}^n \mathcal{U}_{0i}(\theta; X_i, \tilde{T}_i, \tilde{\epsilon}_i), \quad (7)$$

where $\mathcal{U}_{0i}(\cdot; X_i, \tilde{T}_i, \tilde{\epsilon}_i)$ is the derivative of the log-likelihood term for a bivariate Probit model (Ashford and Sowden, 1970) for the event $(\epsilon_{ij} = 1, \tilde{T}_{ij} \leq \tau)$ of the i th twin-pair. A nice property of the Probit random effects model is that the marginal distribution obtained by integrating over the normal distributed random effects is also a multivariate Probit model, and the derivative of the log-likelihood with respect to the parameter vector may in turn be written as a linear combination of bivariate cumulative normal distribution functions. The general derivation may be found in (Holst et al., 2011), and the integration problem related to evaluating the bivariate cumulative distribution functions can be dealt with as described in (Genz, 1992). In principle, the same procedure could be applied to higher-dimensional problems thus allowing us to generalize the modelling framework to larger pedigrees.

We will describe the censoring distribution by its survival function

$$G_c(t_1, t_2; Z_i) = \mathbb{P}(C_{i1} > t_1, C_{i2} > t_2 \mid Z_i), \quad (8)$$

given covariates Z_i observed for all twin-pairs $i = 1, \dots, n$, and we will assume that the failure times are independent of the censoring times given these covariates.

Furthermore, we will assume that we have a correct model for the censoring mechanism with estimate \widehat{G}_c . We then define the IPCW-adjusted estimating equation via the new score

$$\mathcal{U}(\theta; X, Z, \widetilde{T}, \widetilde{\epsilon}) = \sum_{i=1}^n \mathcal{U}_i(\theta; X_i, Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i) = \sum_{i=1}^n \frac{\Delta_{i1}\Delta_{i2}}{\widehat{G}_c(\widetilde{T}_{i1}, \widetilde{T}_{i2}; Z_i)} \mathcal{U}_{0i}(\theta; X_i, \widetilde{T}_i, \widetilde{\epsilon}_i). \quad (9)$$

The censoring mechanism (8) may be modelled using frailty models, but in the case where data arises from a twin registry, censoring will typically be administrative and hence twins are censored at the same time. In this case

$$G_c(t_1, t_2 \mid Z_i) = \mathbb{P}(C_i > t_1 \vee t_2 \mid Z_i) = G_c(t_1 \mid Z_i) \wedge G_c(t_2 \mid Z_i). \quad (10)$$

Therefore, the problem of identifying the bivariate censoring distribution is simplified to just estimating the marginal censoring distributions.

Consistency of the parameter estimates relies on a correctly specified model for the censoring mechanism (10), which would suggest a quite rich semi-parametric model for the marginal censoring distributions. However, a computational limitation of the semi-parametric approach is, that the calculation of asymptotic standard errors (from the estimated influence functions as described below) is quite computational intensive in the order $\mathcal{O}(nK)$ where K is the number of event times and n the number of subjects. In large registry studies a sufficiently flexible parametric survival model may therefore be preferable. We note that asymptotic double-robustness could be obtained by adding an augmentation term to the estimating equation (Tsiatis, 2006) requiring just one of the two models to be correct to obtain consistency. In the following, we will, however, assume that G_c lies within a parametric family and let $\widehat{\gamma}$ be a consistent estimator such that $\widehat{G}_c(\cdot; z) = \widehat{G}_c(\cdot; z, \widehat{\gamma})$.

Theorem 1. *Let $\{T_i, C_i, \epsilon_i, X_i, Z_i\}$ be iid and $\widehat{\gamma}$ a consistent regular asymptotic linear estimator for the parametric censoring distribution. Denote the right-hand-side terms of (9) as $\mathcal{U}_i(\theta_0, \gamma_0)$. Under the following regularity conditions*

1. *In a neighbourhood of $(\theta_0^T, \gamma_0^T)^T$ the function \mathcal{U}_i is twice continuously differentiable with $\mathbb{E}(-\partial \mathcal{U}(\theta_0, \gamma_0)/\partial \theta)$ being positive-definite.*
2. *The censoring times (C_{1i}, C_{2i}) are conditionally independent of $(T_{1i}, T_{2i}, \epsilon_{1i}, \epsilon_{2i})$ implying $G_c(t_1-, t_2-; z) = \mathbb{E}(\Delta_{1i}\Delta_{2i} \mid T_{1i} = t_1, T_{2i} = t_2, Z_i = z)$.*
3. *$\mathbb{P}(T_{1i} > \tau, T_{2i} > \tau) > 0$*
4. *The covariates X_i, Z_i are bounded.*
5. *$G_c(t_1, t_2; z) > 0$ with probability 1 for $t_1, t_2 \in [0, \tau]$.*

the estimator $\widehat{\theta}$ obtained as the root of (9) is consistent and asymptotically normal.

Consistency follows from condition 1-3 by noting that for any term on the right-hand-side of (9), we obtain for known censoring distribution:

$$\begin{aligned} \mathbb{E}[\mathcal{U}_i(\theta; X_i, Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i)] &= \mathbb{E}\{\mathbb{E}[\mathcal{U}_i(\theta; X_i, Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i) \mid X_i, Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i]\} \\ &= \mathbb{E}\{\mathbb{E}(\Delta_{i1}, \Delta_{i2} \mid Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i) G_c(\widetilde{T}_{i1}, \widetilde{T}_{i2} \mid Z_i)^{-1} \mathcal{U}_{0i}(\theta; X_i, \widetilde{T}_i, \widetilde{\epsilon}_i)\} \\ &= \mathbb{E}[\mathcal{U}_{0i}(\theta; X_i, \widetilde{T}_i, \widetilde{\epsilon}_i)] = 0, \end{aligned}$$

where we actively assumed consistency of both the models (6) and (8). Note that the positive probability of being at risk is fulfilled when the support of the censoring times lies within the support of T_{1i} and T_{2i} . We emphasize that a key regularity condition here is that of positivity (5), namely that the probability of any twin-pair being uncensored is strictly larger than zero. In practice, the probabilities should be sufficiently large to avoid instability of the estimating equation in smaller sample sizes.

We now sketch the calculation of the asymptotic standard errors of the estimator. The estimator for $\hat{\gamma}$ will typically be a GEE-type m -estimator since we will use both twins to estimate the marginal censoring distribution. This implies asymptotic linearity:

$$\sqrt{n}(\hat{\gamma} - \gamma_0) = n^{-1/2} \sum_{i=1}^n IF_1(\gamma_0; Z_i, \tilde{T}_i, \tilde{\epsilon}_i) + o_p(1),$$

where IF_1 is the influence function of the estimator (Stefanski and Boos, 2002).

Let $\hat{\theta}(\hat{\gamma})$ be the two-stage estimator obtained by finding the root of (9) with the plugin-estimate of the censoring distribution via $\hat{\gamma}$. The conditions of Theorem 1 implies that the empirical averages of the derivatives of the score converges to their corresponding expectations, and a Taylor expansion of (9) around the true parameters θ_0 and γ_0 , shows that

$$\begin{aligned} \sqrt{n}(\hat{\theta}(\hat{\gamma}) - \theta_0) &= n^{-1/2} \sum_{i=1}^n IF_2(\theta_0; X_i, Z_i, \tilde{T}_i, \tilde{\epsilon}_i) \\ &\quad + n^{-1/2} \mathbb{E}\left[\frac{\partial}{\partial \theta} \mathcal{U}_i(\theta_0, \gamma_0)\right]^{-1} \mathbb{E}\left[\frac{\partial}{\partial \gamma} \mathcal{U}_i(\theta_0, \gamma_0)\right] \sum_{i=1}^n IF_1(\gamma_0; Z_i, \tilde{T}_i, \tilde{\epsilon}_i) + o_p(1) \quad (11) \\ &= n^{-1/2} \sum_{i=1}^n IF_3(\theta_0; X_i, Z_i, \tilde{T}_i, \tilde{\epsilon}_i) + o_p(1), \end{aligned}$$

where the first term corresponds to the iid decomposition for known censoring distribution

$$\sqrt{n}(\hat{\theta}(\gamma_0) - \theta_0) = n^{-1/2} \sum_{i=1}^n IF_2(\theta_0; X_i, \tilde{T}_i, \tilde{\epsilon}_i) + o_p(1). \quad (12)$$

The influence functions may be estimated from the bi-products of the Newton-Raphson optimization, as the matrix product of the derivative of the score times the score itself. We refer to Holst et al. (2011) for expressions for the relevant terms of IF_2 , which are implemented in the `metS` R-package (Holst and Scheike, 2014).

It follows from (11) that the two-stage estimator is asymptotically normal and the asymptotic variance of (11) can be estimated by plugging in the parameter estimates

$$\frac{1}{n} \sum_{i=1}^n IF_3(\hat{\theta}, \hat{\gamma}; X_i, Z_i, \tilde{T}_i, \tilde{\epsilon}_i)^{\otimes 2}.$$

Similar results can be shown in the general case where \widehat{G}_c is an asymptotically linear consistent estimator of the censoring distribution, such that

$$\sqrt{n} \left[\widehat{G}_c(t_1, t_2; Z) - G_c(t_1, t_2; Z) \right] = n^{-1/2} \sum_{i=1}^n IF_{G_c}(t_1, t_2, Z; Z_i, \widetilde{T}_i, \widetilde{\epsilon}_i) + o_p(1),$$

where the iid terms IF_{G_c} are the influence functions. For the choice of a Cox-regression, the proof of the consistency and asymptotic normality of the IPCW estimator follows along the lines of Scheike et al. (2008) or Lin (2000).

In the case of a Kaplan-Meier estimator the linear expansion above follows from Gill (1980); see also Section IV.3.2 of Andersen et al. (1993). In the case of a Cox model the linear expansion is a consequence of the results in Section VII.2.2 and VII.2.3 of Andersen et al. (1993). Specific technical assumptions are also given there. Here, the focus is on the use of parametric models due to the computational advantages.

3.2. Model Selection and Testing

The main hypothesis in most applications of the Liability Threshold model will be to *a)* Test for a genetic component *b)* Quantify this effect. The first problem should generally not be examined in the polygenic model to avoid in part the many genetic model assumptions and in part the difficulties of testing parameters on the boundary of the parameter space. A reasonable modelling approach is generally to initially estimate a more flexible model, where we instead of a random effects model estimate the parameters of a bivariate Probit model

$$\mathbb{P}(T_1 \leq \tau, T_2 \leq \tau \mid \epsilon_1 = 1, \epsilon_2 = 1, \mid X_1, X_2) = \Phi_{\rho_{zyg}}(\beta_{zyg}^T X_1, \beta_{zyg}^T X_2^T), \quad (13)$$

where $\Phi_{\rho_{zyg}}$ is the bivariate normal CDF with mean 0 and variance given by a correlation matrix with correlation coefficient ρ_{zyg} depending on zygosity. A test for identical marginals should be done as a first step, i.e., testing if $\beta_{MZ} = \beta_{DZ}$. Next, a formal test for the presence of a genetic component can be obtained by testing the null hypothesis of identical tetrachoric correlations in MZ and DZ twins $\rho_{MZ} = \rho_{DZ}$. Estimates on the risk scale such as concordance rates are also preferably calculated in this model. Note that while the test for genetic influence still requires assumption of same environmental effects in MZ and DZ twins, the many genetic assumptions of the polygenic model, e.g., linkage equilibrium and that a subset of ACDE fits the data, are no longer necessary.

With evidence of a genetic component, the next step should be to quantify the possible genetic and environmental effects based on the IPCW adjusted Liability Threshold model (6). In population genetics it is common to compare different models using information criteria such as the AIC (Akaike, 1973). In general, the derivation of these measures relies on inference being done within a maximum likelihood framework, and are no longer generally valid in an estimating equation framework. The Quasi-AIC (QIC) has been suggested (Pan, 2001) in the GEE framework. However, in the case of (6) the estimating equation corresponds to the weighted score-function of the complete-data likelihood

$\sum_{i=1}^n \log L_i(\theta; X_i, \tilde{T}_i, \tilde{\epsilon}_i)$ from which (7) is obtained. It follows that

$$\mathbb{E} \left[\frac{\Delta_{i1} \Delta_{i2}}{G_c(T_{i1}, T_{i2}; Z_i)} \log L_i(\theta; X_i, \tilde{T}_i, \tilde{\epsilon}_i) \right] = \mathbb{E}(\log L_i(\theta; X_i, \tilde{T}_i, \tilde{\epsilon}_i)),$$

and hence the weighted AIC

$$\text{AIC}_{\text{IPCW}} = 2 \sum_{i=1}^n \frac{\Delta_{i1} \Delta_{i2}}{\widehat{G}_c(T_{i1}, T_{i2}; Z_i)} \log L_i(\theta; X_i, \tilde{T}_i, \tilde{\epsilon}_i) - 2P,$$

where P is the number of parameters in θ , will also provide an approximation of the relative entropy between the estimated model and the true data generating model, and may therefore serve as a model selection tool.

4. Simulation study

We set up a simulation study to examine the properties of our proposed estimator in a realistic setup. The cumulative incidence function for cancer conditional on a random effect η_1 , was chosen as

$$F_1(t \mid \eta_1) = \mathbb{P}(T \leq t, \epsilon = 1 \mid \eta_1) = \Phi_{\sigma_{E_1^2}}(\alpha(t) + \Phi^{-1}(p_1) + \eta_1),$$

with $\alpha(t) = -\exp(10 - 0.15t)$, $p_1 = 0.065$. The inverse link-function $\Phi_{\sigma_{E_1^2}}$ was chosen as a normal CDF with variance $\sigma_{E_1^2} = 1 - \text{Var}(\eta_1)$. This parametrisation leads to a marginal CIF resembling the distribution observed in the real data described in Section 5, with a marginal lifetime prevalence of 0.065 (see Figure 3). The type of cause (cancer or death without cancer) were simulated from a Bernoulli-distribution with probability $F_1(\infty) = \Phi_{\sigma_{E_1^2}}(\eta_1 + \Phi^{-1}(0.065))$, and the event times drawn from $\mathbb{P}(T \leq t \mid \eta_k, \epsilon = k)$ which for the competing risk of death was chosen as the distribution $\Phi_{\sigma_{E_2^2}}(0.1(t - 85) + \eta_2)$, again with a marginal resembling what was observed in the real data example. The random effect structure η_1 was chosen as an ACE-model with the C-component shared across the two competing risks, and with η_2 only consisting of this shared environmental effect $\eta_2 = \eta^C$. Independent censoring was simulated from a Weibull distribution with cumulative hazard $\Lambda_0(t) = (\lambda t)^\nu$, with scale parameter fixed at $\log(\lambda) = -4.5$, and the parameters were estimated using a marginal model with working independence structure.

We simulated 10,000 MZ and 10,000 DZ twin pairs from the above model under three different ACE structures $(\sigma_A^2, \sigma_C^2, \sigma_E^2) \in \{(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}), (\frac{1}{2}, \frac{1}{4}, \frac{1}{4}), (\frac{3}{5}, \frac{1}{5}, \frac{1}{5})\}$, and with varying degree of censoring $\log(\nu) \in \{0.5, 2\}$ corresponding to roughly 59% and 48% right-censoring. In each scenario the naive estimator ignoring censoring was compared to the IPCW-adjusted estimators based on a parametric marginal Weibull model, with standard errors based on the correct influence functions (11) (Weibull₂) and standard errors based on the influence function (12) without adjusting for the uncertainty in the weights (Weibull₁), and an IPCW-adjusted estimator based on the Kaplan-Meier estimator (KM).

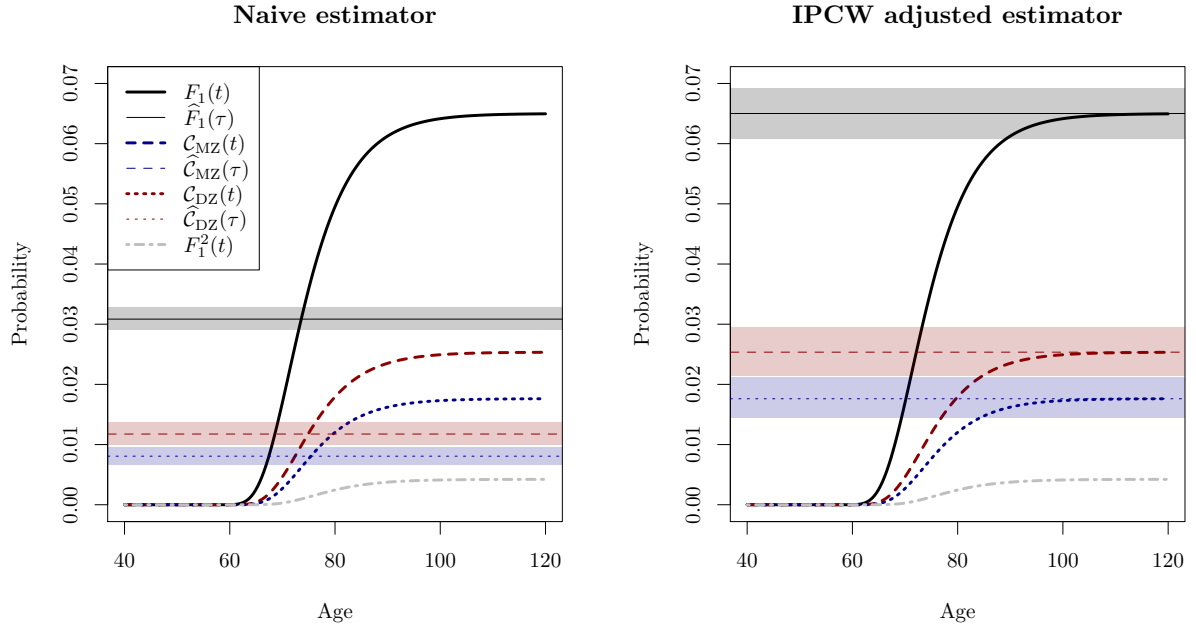


Figure 3: Simulated cumulative incidence and concordance function with $\sigma_A^2 = \sigma_C^2 = \sigma_E^2 = \frac{1}{3}$. Thick lines shows true cumulative incidence for cancer (F_1 , benchmark for perfect dependence), MZ concordance function (\mathcal{C}_{MZ}), DZ concordance function (\mathcal{C}_{DZ}), and the squared cumulative incidence (F_1^2 , benchmark for independence). The thin horizontal lines shows the mean estimates and 2.5% and 97.5% quantiles of 1,000 replications with 20,000 twin pairs and 59% censoring, for the naive estimator ignoring censoring (left panel) and the IPCW adjusted estimator (right panel).

	F_1		\mathcal{C}_{MZ}		\mathcal{C}_{DZ}		σ_A^2		σ_C^2		σ_E^2	
	Av.	Cv.	Av.	Cv.	Av.	Cv.	Av.	Cv.	Av.	Cv.	Av.	Cv.
True	0.065		0.025		0.018		0.333		0.333		0.333	
Naive	0.031	0.000	0.012	0.000	0.008	0.000	0.280	0.888	0.452	0.559	0.267	0.212
Weibull ₁	0.065	0.948	0.025	0.944	0.018	0.956	0.335	0.957	0.331	0.956	0.334	0.940
Weibull ₂	0.065	0.948	0.025	0.944	0.018	0.957	0.335	0.957	0.331	0.956	0.334	0.940
KM	0.065	0.948	0.025	0.944	0.018	0.955	0.335	0.957	0.331	0.955	0.334	0.940
True	0.065		0.030		0.018		0.500		0.250		0.250	
Naive	0.031	0.000	0.014	0.000	0.008	0.000	0.414	0.769	0.386	0.453	0.200	0.273
Weibull ₁	0.065	0.952	0.030	0.952	0.018	0.953	0.498	0.956	0.250	0.956	0.252	0.946
Weibull ₂	0.065	0.952	0.030	0.952	0.018	0.953	0.498	0.956	0.250	0.956	0.252	0.946
KM	0.065	0.954	0.030	0.954	0.018	0.954	0.498	0.957	0.250	0.955	0.252	0.945
True	0.065		0.034		0.018		0.600		0.200		0.200	
Naive	0.031	0.000	0.016	0.000	0.008	0.000	0.491	0.636	0.349	0.365	0.160	0.327
Weibull ₁	0.065	0.946	0.034	0.952	0.018	0.939	0.593	0.950	0.204	0.946	0.203	0.950
Weibull ₂	0.065	0.946	0.034	0.953	0.018	0.942	0.593	0.954	0.204	0.950	0.203	0.951
KM	0.065	0.945	0.034	0.952	0.018	0.939	0.593	0.951	0.204	0.948	0.203	0.952
True	0.065		0.025		0.018		0.333		0.333		0.333	
Naive	0.048	0.000	0.018	0.000	0.012	0.000	0.318	0.951	0.366	0.907	0.315	0.850
Weibull ₁	0.065	0.955	0.025	0.948	0.018	0.951	0.332	0.953	0.333	0.955	0.334	0.949
Weibull ₂	0.065	0.955	0.025	0.948	0.018	0.953	0.332	0.955	0.333	0.956	0.334	0.950
KM	0.065	0.956	0.025	0.950	0.018	0.955	0.333	0.954	0.332	0.954	0.335	0.953
True	0.065		0.030		0.018		0.500		0.250		0.250	
Naive	0.048	0.000	0.021	0.000	0.012	0.001	0.477	0.936	0.287	0.896	0.236	0.865
Weibull ₁	0.065	0.946	0.030	0.965	0.018	0.938	0.496	0.952	0.252	0.945	0.252	0.950
Weibull ₂	0.065	0.946	0.030	0.966	0.018	0.941	0.496	0.958	0.252	0.952	0.252	0.952
KM	0.065	0.958	0.030	0.964	0.018	0.942	0.498	0.957	0.251	0.952	0.251	0.957
True	0.065		0.034		0.018		0.600		0.200		0.200	
Naive	0.048	0.000	0.024	0.000	0.012	0.003	0.570	0.918	0.240	0.877	0.189	0.871
Weibull ₁	0.065	0.952	0.034	0.940	0.018	0.940	0.598	0.922	0.201	0.924	0.201	0.939
Weibull ₂	0.065	0.952	0.034	0.942	0.018	0.966	0.598	0.948	0.201	0.949	0.201	0.944
KM	0.065	0.957	0.034	0.945	0.018	0.941	0.599	0.931	0.200	0.932	0.202	0.948

$\nu = 1.6$
59% cens.

$\nu = 7.4$
48% cens.

Table 1: Simulation based on n=10,000 MZ and DZ twin pairs. Average (Av.) of estimates across 1,000 replications and coverage probabilities (Cv.) of corresponding 95% confidence limits is shown for prevalence (F_1), MZ concordance (\mathcal{C}_{MZ}), DZ concordance (\mathcal{C}_{DZ}), and the variance components σ_A^2 , σ_C^2 and σ_E^2 . Results are shown for the naive estimator not taking the censoring into account (Naive), Weibull IPCW ignoring uncertainty in weights (Weibull₁), Weibull IPCW with correct standard errors (Weibull₂), and Kaplan-Meier without adjustment for uncertainty in weights (KM).

The results of the simulation study are summarized in Table 1 with average estimates and coverage probabilities of the 95% confidence limits reported for the prevalence F_1 , concordance in MZ twins \mathcal{C}_{MZ} , concordance in DZ twins \mathcal{C}_{DZ} , and the variance components σ_A^2 , σ_C^2 , and σ_E^2 . In general the naive estimates where the censoring mechanism is ignored shows very high downward bias with poor coverage in both the prevalence and concordance estimates, which is generally expected. In these simulations the bias of the heritability estimate σ_A^2 is in all cases negative with coverage that performs worse for larger true value of σ_A^2 . As discussed in Scheike et al. (2014a) the direction of the bias in the heritability estimates may, however, go in either direction depending on both the dependence structure and censoring distribution. The intuition for this is, that while the concordance is biased downwards in both the MZ and DZ twins, it may change relatively more/less in the DZ twins.

Generally, the loss in efficiency using the Kaplan-Meier estimator seemed to be very modest. Interestingly, the two IPCW-adjusted estimators ignoring the uncertainty in the estimated weights (KM and Weibull₁) showed excellent coverage probabilities across almost all scenarios. This may be explained by the high degree of censoring (as also seen in the real data), which causes the variance of the estimator to be dominated by the variance of the estimator based on (9) where only the uncensored pairs are used. A tendency was in fact seen towards slightly smaller coverage when the censoring was smaller and heritability higher, while the estimator with confidence limits based on (11) performs seemingly better here. Ignoring the estimated censoring probabilities can in some situations lead to conservative estimates (Rotnitzky and Robins, 1995). This does not seem to be the case here, and may be a consequence of the estimator of the censoring distribution being a GEE-type estimator and not a MLE.

We also examined the effect of introducing a covariate affecting both the censoring and transition probabilities to death or cancer. Given a normal distributed covariate $X \sim \mathcal{N}(0, 0.25)$, the shared environmental effect (C component) was defined as $\eta^C = 0.5X + \eta^{C_0}$ with $\eta^{C_0} \sim \mathcal{N}(0, \sigma_C^2 - 0.0625)$, and the random effect for the competing risk of death was defined as $\eta_2 = \eta_C - 0.25X$. For the censoring mechanism we used a proportional hazards model with baseline hazard as described above, with shape-parameter $\log(\nu) = 0.5$, such that the cumulative hazard took the form $\Lambda(t) = \Lambda_0(t) \exp(-X)$. Results are summarized in Table 2, and are generally very comparable to the results of Table 1.

5. Application to twin cancer data

Studying genetic influence on the complex trait of cancer is central in themes of etiology, treatment and prevention. Twin and general family studies have reported low to moderate genetic influence (Lichtenstein et al. (2000) and Baker et al. (2005)). Based on a combined Nordic study of the Danish, Finnish and Swedish twins registries, Lichtenstein et al. (2000) concluded that 42% of variation in prostate-cancer liability was due to genetic factors (95% confidence limits 0.29–0.50). However, in these cohorts around 70% of the participants are censored resulting in biased estimates of all population parameters including prevalences, concordances rates and heritability, as discussed in the previous sections.

	True	IPCW			Naive		
		Av.	Cov.	MSE	Av.	Cov.	MSE
F_1	0.065	0.065	0.962	0.0004	0.035	0.000	0.0916
ρ_{MZ}	0.667	0.664	0.970	0.0746	0.736	0.160	0.5282
ρ_{DZ}	0.500	0.499	0.951	0.1343	0.600	0.107	1.0914
\mathcal{C}_{MZ}	0.025	0.025	0.974	0.0003	0.014	0.000	0.0137
\mathcal{C}_{DZ}	0.018	0.018	0.951	0.0003	0.010	0.000	0.0065
$\lambda_{R,MZ}$	6.000	5.971	0.955	13.562	11.347	0.000	2897.3
$\lambda_{R,DZ}$	4.172	4.171	0.954	12.133	7.976	0.000	1484.2
$\log(\text{OR})_{MZ}$	2.670	2.660	0.968	1.7900	3.373	0.000	50.969
$\log(\text{OR})_{DZ}$	1.942	1.940	0.955	2.1320	2.662	0.004	53.658
σ_A^2	0.333	0.330	0.953	0.8823	0.272	0.866	0.9011
σ_C^2	0.333	0.334	0.946	0.6352	0.464	0.427	2.1052
σ_E^2	0.333	0.336	0.967	0.0746	0.264	0.137	0.5282
F_1	0.065	0.065	0.941	0.0005	0.035	0.000	0.0921
ρ_{MZ}	0.750	0.748	0.941	0.0618	0.804	0.213	0.3272
ρ_{DZ}	0.500	0.499	0.949	0.1396	0.601	0.108	1.0966
\mathcal{C}_{MZ}	0.030	0.030	0.948	0.0004	0.016	0.000	0.0196
\mathcal{C}_{DZ}	0.018	0.018	0.943	0.0003	0.010	0.000	0.0065
$\lambda_{R,MZ}$	7.166	7.154	0.944	17.438	13.565	0.000	4144.1
$\lambda_{R,DZ}$	4.172	4.173	0.947	13.063	7.996	0.000	1500.3
$\log(\text{OR})_{MZ}$	3.118	3.113	0.943	2.1903	3.824	0.000	51.544
$\log(\text{OR})_{DZ}$	1.942	1.939	0.945	2.2416	2.664	0.000	54.034
σ_A^2	0.500	0.499	0.945	0.8144	0.407	0.716	1.3176
σ_C^2	0.250	0.249	0.944	0.6247	0.397	0.332	2.5247
σ_E^2	0.250	0.252	0.938	0.0618	0.196	0.169	0.3272
F_1	0.065	0.065	0.952	0.0005	0.035	0.000	0.0919
ρ_{MZ}	0.800	0.799	0.949	0.0476	0.845	0.239	0.2205
ρ_{DZ}	0.500	0.499	0.955	0.1368	0.600	0.114	1.0871
\mathcal{C}_{MZ}	0.034	0.034	0.951	0.0005	0.018	0.000	0.0243
\mathcal{C}_{DZ}	0.018	0.018	0.939	0.0003	0.010	0.000	0.0065
$\lambda_{R,MZ}$	7.987	7.988	0.956	17.964	15.101	0.000	5109.9
$\lambda_{R,DZ}$	4.172	4.175	0.956	12.758	7.983	0.000	1489.1
$\log(\text{OR})_{MZ}$	3.441	3.442	0.951	2.3085	4.147	0.000	51.565
$\log(\text{OR})_{DZ}$	1.942	1.940	0.955	2.1908	2.662	0.000	53.664
σ_A^2	0.600	0.600	0.954	0.7214	0.489	0.596	1.6372
σ_C^2	0.200	0.199	0.958	0.5866	0.356	0.262	2.7722
σ_E^2	0.200	0.201	0.945	0.0476	0.155	0.178	0.2205

Table 2: Simulation based on $n=10,000$ MZ and DZ twin pairs with continuous covariate affecting both the censoring mechanism and the transition probabilities to cancer and death. Average (Av.) of estimates across 1,000 replications, coverage probabilities (Cv.) of corresponding 95% confidence limits, and Mean Squared Error multiplied by 100 (MSE) is shown for prevalence (F_1), concordance (\mathcal{C}_{MZ} , \mathcal{C}_{DZ}), relative recurrence risks ratios ($\lambda_{R,MZ}$, $\lambda_{R,DZ}$), and log odds-ratios ($\log(\text{OR})_{MZ}$, $\log(\text{OR})_{DZ}$), and the variance components σ_A^2 , σ_C^2 and σ_E^2 . Results are shown for the naive estimator ignoring the censorings (Naive), and Weibull IPCW using a correct model for the censoring (IPCW).

We investigate genetic influence on prostate cancer using the population based twin cohort of Danish twins born 1900 to 1982 constituting $N = 15,509$ male pairs of whom 5,488 MZ and 10,021 same sex male DZ pairs are eligible for studying prostate cancer. The cohort is followed up with respect to survival status as of July 2009. Data on cancer diagnosis, status and time of event, were obtained from the National Cancer Registry which was initiated in 1943 (See Hjelmberg et al. (2014) for further description of the cohort). Numbers of pairs by status of cancer and death can be seen in Table 3.

MZ & DZ	Number of pairs at time of follow-up		
	Prostate cancer	No cancer and dead	No cancer and alive
Prostate cancer	25 & 14	178	108
No cancer and dead	70	843 & 1,694	1,319
No cancer and alive	39	492	4,019 & 6,708

Table 3: Number of pairs by status at time of follow-up with MZ pairs in lower left triangle and DZ pairs in upper right triangle.

There was a significant difference in the censoring distributions in MZ and DZ twins. This may in part be explained by increased used of In Vitro Fertilizations over time which have caused a change in DZ/MZ distribution and perhaps consequently also censoring distributions in this cohort. We therefore based the IPCW-model on a stratified Kaplan-Meier model.

As described in Section 3.2 we first examined if the marginal distributions within MZ and DZ twins could be assumed to be the same ($p=0.52$). In the reduced model with identical marginals the tetrachoric correlations was 0.63 (0.47–0.75) for MZ pairs and 0.25 (0.07–0.41) for DZ pairs. A test for genetic effects was performed by comparing these correlation coefficients which yielded a p-value of $p=0.001$, indicating strong evidence in support of a genetic contribution. In the polygenic models the AIC_{IPCW} was slightly in favour of the ADE model but very similar results was obtained from AE and ACE models in terms of broad-sense heritability. For the chosen ADE model the broad-sense heritability was 0.63 (0.49–0.77). The results are summarized in Table 4 together with the biased naive estimates as a reference. Here we also report the *casewise concordance* (Witte et al., 1999), i.e., the conditional probability that a twin gets cancer given the co-twin got cancer, and the *relative recurrence risk ratio* which describes the excess risk of prostate cancer for a twin given the co-twin got prostate cancer, compared to the marginal (population) risk

$$\lambda_R = \frac{\mathbb{P}(T_1 \leq \tau, T_2 \leq \tau, \epsilon_1 = 1, \epsilon_2 = 1)}{\mathbb{P}(T_1 \leq \tau, \epsilon_1 = 1)^2}.$$

All estimates except for the heritability are reported from the more parsimonious bivariate Probit model but results was almost identical with the estimates from the ADE-model.

In conclusion, we see strong evidence for a genetic component in the development of prostate cancer. As expected, the naive estimator provides heavily downward biased

estimates of the prevalence and concordance, and in this case upward bias of the heritability estimates and relative recurrence risk ratio estimates.

	IPCW-adjusted	Naive
F_1	0.055 (0.049; 0.062)	0.015 (0.014; 0.017)
ρ_{MZ}	0.626 (0.466; 0.746)	0.730 (0.629; 0.807)
ρ_{DZ}	0.248 (0.068; 0.412)	0.350 (0.224; 0.465)
\mathcal{C}_{MZ}	0.019 (0.013; 0.027)	0.005 (0.004; 0.007)
\mathcal{C}_{DZ}	0.007 (0.004; 0.013)	0.001 (0.001; 0.002)
\mathcal{C}_{MZ}/F_1	0.340 (0.241; 0.455)	0.324 (0.240; 0.421)
\mathcal{C}_{DZ}/F_1	0.130 (0.076; 0.215)	0.087 (0.053; 0.140)
$\lambda_{R,MZ}$	6.166 (4.132; 8.201)	21.17 (15.25; 27.10)
$\lambda_{R,DZ}$	2.360 (1.148; 3.571)	5.713 (2.966; 8.459)
H^2	0.626 (0.486; 0.766)	0.73 (0.642; 0.819)

Table 4: Estimates (and 95% confidence limits) of association of prostate cancer for MZ and DZ twins based on bivariate Probit model. The first column contains the IPCW-adjusted estimates and the second column the biased estimates ignoring the right-censoring mechanism. We show estimates of prevalence F_1 , tetrachoric correlations ρ , concordance \mathcal{C} , casewise concordance \mathcal{C}/F_1 , and relative recurrence risk ratio λ_R . The broad-sense heritability estimate H^2 is based on an ADE-model.

We also examined how the association between MZ and DZ twins might depend on age by choosing different values of τ in (5), with different parameters at each time point. As shown in Figure 4, this allows us to describe the cumulative incidence function for prostate cancer and the concordance functions and relative recurrence risk ratios as functions of age based on the flexible bivariate Probit model. We also calculated the heritability for both an ACE and ADE model (Figure 5) which in agreement indicates higher genetic contribution in earlier ages. This stronger dependence in early-onset has been suggested for several types of cancers.

6. Discussion

There has been considerable interest in quantifying the genetic influence of cancer, and family and twin studies have here served as important tools. The censoring problem we have discussed in this paper seems to have been largely ignored in the epidemiological literature, which makes estimates from these studies difficult to interpret.

We have here presented a simple method based on inverse probability weighting that corrects for a major source of bias by taking advantage of the time to event information that is most often provided in cohort studies along with the binary disease status. The method allows for flexible and computational robust modelling of twin dependence at different ages. Our simulations show that the method performs very well in a realistic setup.

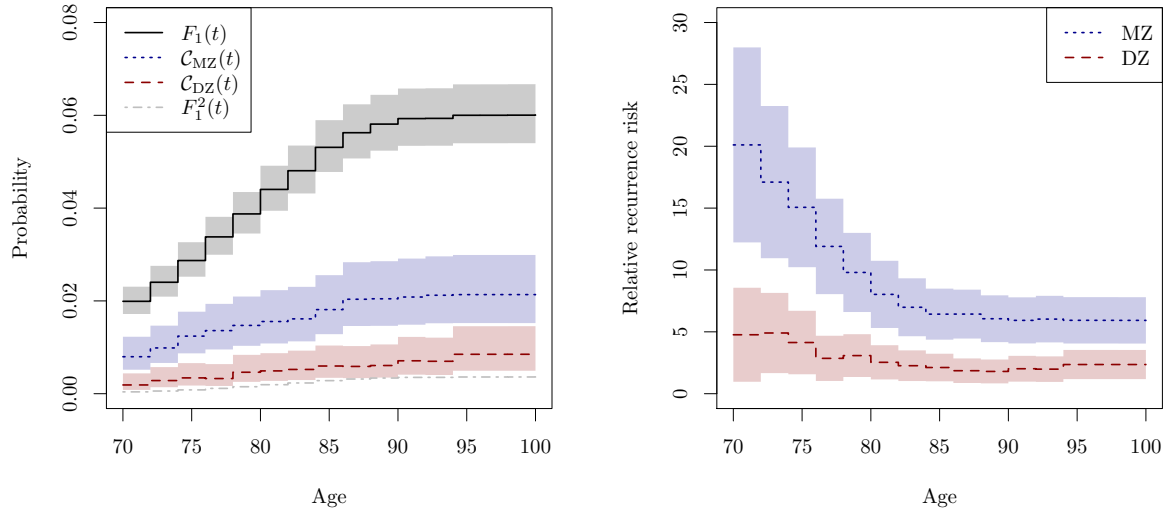


Figure 4: Concordance and relative recurrence risk ratio estimates for prostate cancer in MZ and DZ twins. The left panel shows the concordance for prostate cancer in MZ and DZ twins with point-wise 95% confidence limits calculated at different ages in two-years intervals. The two concordance functions are bounded above by the marginal cumulative incidence corresponding to perfect dependence and below by the squared marginal corresponding to independence. In the right panel the relative recurrence risk ratio is shown for MZ and DZ twins for different ages with point-wise 95% confidence limits.

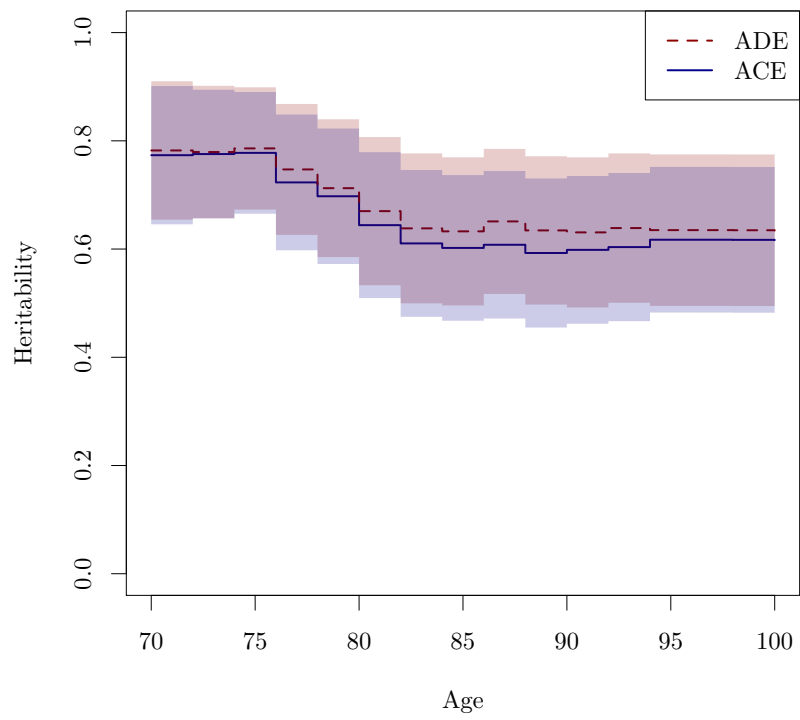


Figure 5: Heritability of prostate cancer calculated at different ages in two years intervals with point-wise 95% confidence limits. Estimates are based on IPCW adjusted ACE (solid line) and ADE (dashed line) models.

Applied on data from the Danish Twin Registry and Danish Cancer Registry we estimated a heritability of 0.62 in prostate cancer, and relative recurrence risk ratios of 6.2 in MZ twins and 2.4 in DZ twins.

Here we have only considered twins but both the estimation and computational framework can be generalized to larger pedigrees. Also, extensions to ascertained samples should follow along the lines of Javaras et al. (2010). Another topic for future research will be development of efficient and robust estimating equations.

All methods are available in the R package **metS** (Holst and Scheike, 2014).

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